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Filing Date	Jan 5, 2001
First Named Inventor	Walke, D. Wade
Group Art Unit	1652
Examiner Name	C. Fronda
Attorney Docket Number	LEX-0114-USA

ENCLOSURES *(check all that apply)*

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment / Reply
  - [x] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
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- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
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- [ ] After Allowance Communication to Group
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- [ ] Proprietary Information
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- [x] Other Enclosure(s) *(please identify below):*
  - Return Postcard
  - Exhibits A - D

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Signature		Date	May 6, 2003

EXPEDITED PROCEDURE
EXAMINING GROUP 1652

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Walke *et al.*	Group Art Unit: 1652	
Application No.:	09/755,016	Examiner: C. Fronda	
Filed:	01/05/2001	Atty. Docket No.: LEX-0114-USA	

Title: Novel Human Proteases and Polynucleotides Encoding the Same

RESPONSE TO OFFICE ACTION DATED MARCH 6, 2003

Box AF
Commissioner for Patents
Alexandria, VA 22313

Sir:

The Applicants acknowledge the receipt of the Office Action ("the present Action") mailed on March 6, 2003 (Paper No. 15), which has been carefully reviewed and studied. Reexamination and reconsideration of the application is requested in view of the following remarks. In order to facilitate the Examiner's evaluation of the application, Applicants have attempted to address the rejections in Paper No. 15 in the same order in which they were originally raised.

The two month deadline for filing a response to a Final Office Action as set forth in Manual of Patent Examination Procedure, Section 706.07(f)(A), is May 6, 2003. The response is thus timely filed,

RESPONSE

I. Status of the Claims

No claims have been cancelled. No claims have been amended. No new claims have been added. Claims 1-2 and 5-10 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**.

II. Rejection of Claims 1, 2 and 5-10 Under 35 U.S.C. § 101

The Action first rejects claims 1, 2 and 5-10 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

As set forth in Applicants' response mailed on December 4, 2002 ("the previous response") to the previous Office Action in this case, which was mailed on September 9, 2002 ("the previous Action"), the present invention has a number of substantial and credible utilities, not the least of which is in forensic analysis, as described in the specification, at least at page 10, lines 13-24. However, this utility was not considered **at all** by the Examiner in the present Action. As described in the specification at page 15, lines 20-30, the present sequences define a number of coding single nucleotide polymorphisms - specifically: a C/T polymorphism at nucleotide position 28 of SEQ ID NO:3, a silent polymorphism that results in a leucine at amino acid position 10 of SEQ ID NO:4; and a G/A polymorphism at nucleotide position 379 of SEQ ID NO:3, which can result in an alanine or threonine at amino acid position 127 of SEQ ID NO:4. As such polymorphisms, and particularly combinations of polymorphisms, are the basis for forensic analysis, which does not require <u>any information at all</u> about the ultimate biological function of the encoded protein, and is undoubtedly a "real world" utility, the present sequences <u>must</u> in themselves be useful.

It is important to note that the presence of <u>more</u> useful polymorphic markers for forensic analysis would not mean that the present sequences <u>lack</u> utility. As clearly stated by the Federal Circuit in *Carl* [illegible] 20 USPQ2d [illegible] 1991)

[illegible] be useful to some extent and in certain applications [illegible] The fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a

lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Just because other polymorphic sequences from the human genome have been described does not mean that the use of the presently described polymorphic markers for forensic analysis is not a specific utility.

Applicants respectfully point out that the presently described polymorphisms are useful in forensic analysis **without any further experimentation** - specifically, to specifically identify individual members of the human population based on the presence or absence of the described polymorphism. Simply because the use of these polymorphic markers will necessarily provide additional information on the percentage of particular subpopulations that contain one or more of these polymorphic markers does not mean that additional research is needed in order for these markers as they are presently described in the instant specification to be of use to forensic science. Using the polymorphic markers as described in the specification as originally field will definitely distinguish members of a population from one another. In the worst case scenario, each of these markers are useful to distinguish 50% of the population (in other words, the marker being present in half of the population). The ability to eliminate 50% of the population from a forensic analysis **clearly** is a real world, practical utility. As set forth in *In re Langer* (183 USPQ 288 (CCPA 1974); "*Langer*"):

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

[illegible]

[illegible] *Hoffman v. Klaus*, 9[illegible]

(Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 10, line 18, the present nucleotide sequence has a specific utility in "determining the genomic structure" of the protein encoding regions of the corresponding human chromosome. This is evidenced by the fact that SEQ ID NO:3 can be used to map the 5 coding exons on chromosome 12 (present within the chromosome 12 clone described in Genbank Accession Number AC008121; the alignment and the first page from the Genbank report are presented in **Exhibit B**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 12 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Applicants respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence, as described above. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The specification details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics"

those skilled in the relevant biological and biochemical arts. For further evidence in support of the

Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (2001, Science *291*:1304 *at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

In the previous response, Applicants detailed an additional example of the utility of the present nucleotide sequences, as described in the specification on page 5, lines 9-12, specifically that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. The Action again does not specifically address this assertion of utility, but merely states that "further research" is needed "to identify the biological function and possible diseases associated with the [claimed] nucleic acids", and that this "further research" confirms that the claimed sequences do not have a "real world" utility (Action at page 3). Applicants respectfully point out that, with regard to a "real world" usage, as opposed to the nebulous concept of a "real world" usage expressed by the Examiner in the present and previous Actions, nucleic acid sequences similar to those set forth in SEQ ID NO:3 are used throughout the biotechnology industry every day, for example in such gene chip applications. Applicants are completely at a loss to understand how the Examiner can consider the biotechnology industry, an industrial sector that has a market capitalization of hundreds of billions of dollars, not to be a part of the "real world".

As previously set forth, evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments from genes in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. Affymetrix is clearly a "real world" company, as evidenced the fact that the United States Patent and Trademark Office has issued numerous U.S. Patents to Affymetrix covering gene chip technology, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and

ABI Perkin Elmer, HySeq and Incyte. In addition, two such companies (Agilent acquired by American

Home Products and Rosetta acquired by Merck) were viewed to have such "real world" value that they were acquired by large pharmaceutical companies for significant sums of money. Given the widespread utility of such "gene chip" methods using non-biologically validated, *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* biologically validated coding sequence would have great utility in such DNA chip applications. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Furthermore, compositions that enhance the utility of such DNA chips by specifically identifying biologically validated expressed nucleotide sequences, such as those identified by the presently claimed computer system, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, regarding whether "further research" would be required to practice the claimed invention, Applicants point out that nucleic acid sequences such as SEQ ID NO:3 are routinely used by companies throughout the biotechnology sector **exactly** as they are presented in the Sequence Listing, without **any** further experimentation. Although information regarding the biological activity of a particular nucleic acid sequence might make it even more useful in such applications, this does not mean that the presently described nucleic acid sequences lack a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC*, *supra*).

Additionally, Applicants pointed out in the previous response that a sequence sharing 100% percent identity at the protein level over an extended region of the claimed sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists at the National Center for Biotechnology Information who are *wholly unaffiliated with Applicants* as a "serine protease" (GenBank accession number XM_171629; alignment and GenBank report shown in **Exhibit C**). Applicants point out that an additional sequence sharing almost 100% percent identity at the amino acid level over an even greater length of the described sequence is present in the

XM_208689; alignment and GenBank report shown in **Exhibit D**). Given these two GenBank

annotations, there can be no question that those skilled in the art would clearly believe that Applicants' sequence is a serine protease.

The Action questions Applicants assertion of utility based on homology to proteins of known function, citing articles by Attwood and Miller (2001, Comput. Chem. 25:329-339) and Ponting (2001, Breif. Bioinform. 2:19-29) in an attempt to support this position. The PTO has repeatedly attempted to deny the utility of nucleic acid sequences based on a small number of spurious publications that call into doubt the usefulness of bioinformatic predictions, of which these two articles are merely the latest examples. However, without going into the merits (or lack thereof) of the cited articles, Applicants point out that the lack of 100% unanimous agreement on the usefulness of bioinformatic prediction programs is **completely irrelevant** to the question of whether the claimed nucleic acid sequence has a substantial and specific utility. Applicants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Applicants submit that the overwhelming majority of those of skill in the relevant art would **believe** bioinformatic prediction to be a powerful and useful tool, as evidenced by hundreds if not thousands of journal articles, and would thus **believe** that Applicants sequence is a serine protease. As this is the standard for meeting the utility requirement of 35 U.S.C. § 101, Applicants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not

Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by

numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section III, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, as well as the reasons set forth in the previous response, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1, 2 and 5-10 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

III. Rejection of Claims 1, 2 and 5-10 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1, 2 and 5-10 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1, 2 and 5-10 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Rejection of Claims 1 and 7-10 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1 and 7-10 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

The Action states that claims 1 and 7-10 lack sufficient written description because "there is no disclosure of any particular structure to function/activity relationship" between the claimed fragments of SEQ ID NO:3 and the full length sequence of SEQ ID NO:3 (the Action at page 3). As discussed at length in the previous response, this argument fails to support the alleged lack of written description for at least two reasons. However, since Applicants' assertions were not commented on **at all** in the present Action, they will be repeated here. First, there is a "particular structure to function/activity relationship" disclosed between the claimed fragments of SEQ ID NO:3 and the full length sequence of SEQ ID NO:3 - specifically, that these fragments of SEQ ID NO:3 are **novel**, and therefore **unique**, identifiers of SEQ ID NO:3. The specification, at least at page 5, lines 5-12, details that these fragments can thus be used in a number of different methods, including, but not limited to, in conjunction with PCR to screen libraries, isolate clones, and prepare cloning and sequencing templates, as well as in assessing gene expression patterns using microarray or gene chip formats. Second, and perhaps most importantly, there is **no requirement whatsoever** that novel fragments of a novel sequence have the **exact same function** as the full length sequence in order to be patented. If this were to be the case, hundreds, if not thousands, of issued U.S. Patents would be instantly invalidated, as they each claim nucleotide fragments that have not been demonstrated to have the exact same function as the full length nucleotide sequence. Applicants

("the first response"), to the Office Action mailed on October 26, 2001 ("the First Action"), 35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity [illegible] adequate description of the claimed genus.

California v. Eli Lilly and Co., 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid and amino acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides comprising at least 60 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:3, or a nucleotide sequence that encodes SEQ ID NO:4, are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claims 1 and 7-10 thus meet the written description requirement.

For each of the foregoing reasons, Applicants submit that the rejection of claims 1 and 7-10 under 35 U.S.C. § 112, first paragraph, has been overcome, and request that the rejection be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants

[illegible]

[illegible] that certain amendments of the claims might serve to improve their clarity, a telephone call to the

undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

May 6, 2003
Date

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